UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

003067

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: Jay S. Ellenberger, PM#12
Registration Division (TS-767)

SUBJECT: EPA Registration No. 10182-EUP-RT, PP#9G2200 and FAP9H5217 petition for temporary tolerances of pirimiphos-methyl on stored corn, wheat, rice, and grain sorghum and EPA Registration No. 10182-EUP-RL, PP#9G2154 and FAP9H5201 petition for a temporary tolerance of pirimiphos-methyl on farmer stock peanuts and in peanut oil.

TOX Chemical No. 334B

Background:

The ICI Americas Inc. is requesting to establish tolerances for their organophosphate insecticide pirimiphos-methyl as follows:

Proposed Temporary Tolerances (PP#9G2200)

It is proposed that temporary tolerances be established for combined residues of the insecticide pirimiphos-methyl, O-(2-diethylamino-6-methyl-pyrimidin-4-yl) O,O-dimethyl-phosphorothioate, the metabolite O-(2-ethylamino-6-methyl-pyrimidin-4-yl) O,O-dimethylphosphorothioate and, in free and conjugated form, the metabolites

2-diethylamino-6-methyl-pyrimidin-4-ol
2-ethylamino-6-methyl-pyrimidin-4-ol and
2-amino-6-methyl-pyrimidin-4-ol

in or on the following raw agricultural commodities:

Corn, sorghum and wheat grain	10	ppm
Rice grain	15	ppm
Milk, eggs, poultry, meat, fat and meat byproducts of cattle, goats, hogs, horses, and sheep (except liver and kidney)	0.1	ppm
Liver and kidney	0.5	ppm

Proposed Temporary Tolerances (FAP 9H5217)

It is proposed that temporary tolerances be established for combined residues of the insecticide pirimiphos-methyl, O-(2-diethylamino-6-methyl-pyrimidin-4-yl) O,O-dimethyl-phosphorothioate, the metabolite O-(2-ethylamino-6-methyl-pyrimidin-4-yl) O,O-dimethylphosphorothioate and, in free and conjugated form, the metabolites

2-diethylamino-6-methyl-pyrimidin-4-ol
2-ethylamino-6-methyl-pyrimidin-4-ol and
2-amino-6-methyl-pyrimidin-4-ol

in or on the following raw agricultural commodities:

Rice hulls	60	ppm
Milling fractions of rice and wheat	50	ppm

Proposed Temporary Tolerances (PP#9G2154)

It is proposed that temporary tolerances be established for combined residues of the insecticide pirimiphos-methyl, O-(2-diethylamino-6-methyl-pyrimidin-4-yl) O,O-dimethyl-phosphorothioate, the metabolite O-(2-ethylamino-6-methyl-pyrimidin-4-yl) O,O-dimethylphosphorothioate and, in free and conjugated form, the metabolites

2-diethylamino-6-methyl-pyrimidin-4-ol
2-ethylamino-6-methyl-pyrimidin-4-ol and
2-amino-6-methyl-pyrimidin-4-ol

in or on the following raw agricultural commodities:

Peanuts	25	ppm
Peanut hulls	125	ppm
Milk, eggs, poultry, meat, fat and meat byproduct of cattle, goats, hogs, horses, and sheep (except liver and kidney)	0.1	ppm
Liver and kidney	0.5	ppm

Proposed Food Additive Tolerances (FAP 9H5217)

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Recommendations and Comments:

1. TOXICOLOGY BRANCH (TB) has no objection to establishing the tolerances proposed in PP9G2200 and FAP 9H5217 including tolerances in/on corn, sorghum, rice and wheat grain; secondary tolerances in meat, milk, poultry and eggs; and tolerances in rice hulls and milling fractions of rice and wheat.

TB's favorable recommendation for these tolerances is contingent upon determination by RESIDUE CHEMISTRY BRANCH (RCB) that the tolerance levels as proposed are appropriate and that there will be no specific deferrals from RCB to TB regarding these tolerances.

See the 8 point review attached.

The inerts in the product (ACTELLIC 7E) proposed for use for the EUP program which accompanies PP9G2200 and FAP 9H5217 are not cleared under 40 CFR 180.1001(c) according to TB files. Clearance of the inerts in this product must precede initiation of the EUP program.

2. TB objects to establishing the tolerances proposed in PP9G2154 involving tolerances in/on peanuts at 25 ppm. TB has determined that tolerances for pirimiphos-methyl should not exceed 20 ppm on RACs.

That the tolerance on RACs should not exceed 20 ppm for pirimiphos-methyl is based on the TB rule that the residue level in human food commodities (with "certain exceptions", see below), should not exceed the NOEL for ChE effects in test animals. This rule ensures that acute ChE effects will not occur should an individual consume large amounts of the treated commodity in a short period of time. For the purposes of this rule, it is assumed that an individual in a short span of time (24 hours) may consume up to 1.5 kg of treated commodity (1.5 kg is the average daily amount of food that a 60 kg individual consumes in 24 hours). The calculations are presented below:

TB rule:

$$\frac{\left[\text{Noel for ChE effects in mg/kg/day.}\right] \times 60 \text{ kg}}{1.5 \text{ kg/day}} = \text{Maximal Permissible Residue Level (in mg/kg of diet or ppm).}$$

As applied to pirimiphos-methyl:

$$\frac{0.5 \text{ mg/kg/day} \times 60 \text{ kg}}{1.5 \text{ kg/day}} = 20 \text{ ppm.}$$

Toxicology Branch notes that Registration Division (and presumably the petitioner) was previously informed that any tolerance exceeding 20 ppm in/on peanuts would be unacceptable to Toxicology Branch. See TB review on 10182-EUP-15, PP 9G2154 and FAP 9H5201; by J. Doherty, dated September 25, 1980.

The "certain exceptions" referred to above include food additive type residues (such as occur in peanut oil and in milling fractions of rice and wheat) for which TB believes there is negligible likelihood of an individual ingesting large amounts of the processed quantity in a short span of time. Thus, TB does not object to the proposed tolerance in FAP 9H5217 involving residues in peanut oil.

3. The hen subchronic neurotoxicity study was reviewed and found to be CORE GUIDELINES. It was determined that pirimiphos-methyl does not induce a TOCP-like neurotoxicity in hens receiving 90 doses of 10 mg/kg (HDT).

The problem of the possibility that pirimiphos-methyl causes a TOCP type delayed neuropathy is considered resolved and that pirimiphos-methyl does not, based on available information, induce such a delayed neuropathy.

4. Two mutagenicity studies were submitted and reviewed (a mammalian cell transformation test and a cytogenic study in rats) and found to be negative for mutagenesis.

TB previously requested the registrant to submit an Ames test, but the registrant has not provided EPA with this study. In this current submission (Section C of EPA Acc. No. 071451), the registrant asserts that "there is no scientific justification for repeating this purely predictive Ames test."

TB does not concur with the registrant's conclusion and requests that an Ames test with technical pirimiphos-methyl be conducted and submitted to EPA.

TB is concerned with a possible positive response in this type of test because a previous test gave indications of a positive response (see J. Doherty review, dated Feb. 21, 1980).

This requirement for an acceptable Ames test must be filled ~~resolved~~ prior to granting permanent tolerances for pirimiphos-methyl.

5. Acute toxicity studies and a skin sensitization study on the formulated product ACTELLIC 7E Insecticide (formulation code GFU 053) were reviewed and with the exception of the acute inhalation study, were found to be CORE MINIMUM or better.

The acute inhalation LC_{50} study was determined not to be useful in assessing the inhalation hazard of pirimiphos-methyl. No definite signs of toxicity were noted in the "exposed rats" and it is questionable if the pirimiphos-methyl actually entered the exposure chamber. For example, the atmospheric concentration was reported as "nominal concentration" and actual atmospheric concentrations were not determined.

Before a permanent registration of this product is approved by TB, the inhalation study must be repeated and determined to adequately assess the inhalation toxicity to rats. It is recommended that methods similiar to the actual equipment used to make a spray mist of this product in actual practice be used in the inhalation LC_{50} study.

6. The label for ACTELLIC 7E Insecticide was reviewed and it was determined that the signal word WARNING (based on eye and skin irritation) and the precautionary statements are appropriate.

7. The registrant should be advised that a teratology study in a second species is a requirement for approval of permanent tolerances with pirimiphos-methyl.

8 POINT REVIEW

[Prepared June 1983 for PP#9G2200 and FAP9H5217 concerning pirimiphos-methyl in corn, sorghum, rice and wheat grain and related tolerances.]

1. Toxicological data considered in setting these tolerances included:

Subacute and chronic studies:

90-Day rat feeding	NOEL = 8 ppm (ChE and systemic)
90-Day dog feeding	NOEL <2 mg/kg/day (ChE) (LDT) NOEL = 2 mg/kg/day (systemic)
Mouse oncogenesis (oral)	Negative for oncogenic effects, NOEL between 5 and 250 ppm for ChE inhibition

2-Year dog chronic feeding	NOEL = 0.5 mg/kg/day (ChE) NOEL = 2.0 mg/kg/day (systemic)
2-Year rat chronic feeding, oncogenesis	NOEL = 10 ppm (ChE) NOEL = 300 ppm (systemic) Negative for oncogenic effects
Teratology - rabbits	Negative at 16 mg/kg/day (HDT)
3-Generation Reproduction - rats	NOEL = 100 ppm (HDT)
Acute Neurotoxicity - hens	Equivocal Results
90-Day Neurotoxicity - hens	No neurotoxic effect at 10 mg/kg/day for 90 doses. (HDT)

2. Data considered desirable but currently lacking.

None.

3. Not applicable for this petition.

4. See computer printout attached.

5. Granting this tolerance would increase the % of the ADI used up from 0.08% to 71.00% (see computer printout attached). The TMRC will change from .0023 mg/day (1.5 kg) to 2.1301 mg/day (1.5 kg).

6. The 2-year rat feeding study with a NOEL of 10 ppm for ChE inhibition and a safety factor of 10 were used to determine the ADI etc. The ADI is 0.05 mg/kg/day and the MPI is 3.00 mg/day/60 kg person.

7. Toxicology Branch has no knowledge of pending regulatory actions against registration of pirimiphos-methyl.

8. None.

File last updated 6/21/83

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ACCEPTABLE DAILY INTAKE DATA

RAT,Older NOEL mg/kg	ppm	S.F.	ADI mg/kg/day	MPI mg/day(60kg)
0.500	10.00	10	0.0500	3.0000

Published Tolerances

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Kiwi Fruit(204)	5.000	0.03	0.00225

MPI	TMRC	% ADI
3.0000 mg/day(60kg)	0.0023 mg/day(1.5kg)	0.08

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Current Action 902200

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Corn,all types(38)	10.000	2.51	0.37650
Sorgnum(147)	10.000	0.03	0.00450
Wheat(170)	10.000	10.36	1.55442
Rice(137)	15.000	0.55	0.12417
Eggs(54)	0.100	2.77	0.00416
Milk&Dairy Products(93)	0.100	28.62	0.04292
Meat,inc poultry(89)	0.100	13.85	0.02077
Kidney(203)	0.500	0.03	0.00023
Liver(211)	0.500	0.03	0.00023

MPI	TMRC	% ADI
3.0000 mg/day(60kg)	2.1301 mg/day(1.5kg)	71.00

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7/5/83

STUDIES REVIEWED

A. With technical grade pirimiphos-methyl.

Study	Result	CORE Classificatio
90-day subchronic delayed neurotoxicity with chickens	Not neurotoxic at up to and including 10 mg/kg/day (HDT) for 90 doses.	GUIDELINES
Mutagenesis: Mammalian Cell transformation test	Negative	N/A
Mutagenesis: Cytogenic study in rats	Chromosome gaps noted at 320 mg/kg/day for five days, but no other aberrations noted. Not considered to be a positive mutagenic response.	N/A

B. With formulation GFU 053 (75.4% Pirimiphos-methyl)

Acute oral LD_{50} - rats	2.1 (1.9-2.5) ml of formulation/kg, TOX Cat. III	GUIDELINES
Acute dermal LD_{50} - rabbits	2.0-3.2 ml formulation/kg for males. >3.2 ml formulation/kg females. TOX Cat III	MINIMUM
Primary Eye Irritation - rabbits	Corneal opacity persistent to day 14, TOX Cat. II	GUIDELINES
Primary Dermal Irritation - rabbits	Some irritation persisting to 15 days. TOX Cat. II.	GUIDELINES
Inhalation LC_{50} - rats - (4 hours)	>0.75 mg/l (nominal concentration).	SUPPLEMENTARY

Sensitization study - guinea pigs	Not positive	MINIMUM

The subchronic delayed neurotoxicity of pirimiphos-methyl to the domestic hen.

Huntingdon Research Center, # ICI 411NT/821118, Feb. 4, 1983, EPA Acc. No. 071451, Tab C1.

10 groups of 10 hens (Gallus gallus domesticus), aged 14 months (approx.), were grouped as follows:

Group

1	Vehicle control (corn oil)
2	Untreated control
3	Positive control (TOCP, 7.5 mg/kg/day)
4	Pirimiphos-methyl 0.5 mg/kg/day
5	Pirimiphos-methyl 1.0 mg/kg/day
6	Pirimiphos-methyl 2.5 mg/kg/day
7	Pirimiphos-methyl 5.0 mg/kg/day
8	Pirimiphos-methyl 10.0 mg/kg/day
9*	Pirimiphos-methyl 5.0 mg/kg/day
10*	Pirimiphos-methyl 10.0 mg/kg/day

The pirimiphos-methyl used for this study was from issue 002 or RS/78/G. The purity was not stated. The individual doses were determined on the basis of the daily weight of each bird. Each bird received a total of 90 doses by gavage. In some cases for the higher doses, it was necessary to allow a few days between dosing in order to prevent killing the birds. *Groups 9 and 10 were allowed 90 days to recover from any lesions which might have been induced by the pirimiphos-methyl treatment.

Results:

1. Stability of pirimiphos-methyl in corn oil. The chemical was shown to be stable in corn oil for up to 10 days. The concentrations of pirimiphos-methyl were shown to be within 8% of the nominal concentrations.

2. Mortalities - 18 of the birds died during the 90-day dosing period. None were in the untreated or vehicle control groups. 4 of 10 of the birds dosed with 10 mg/kg (in each group) died.

A single bird dosed with 1.0 mg/kg of pirimiphos-methyl died; 3 birds in the 2.5 mg/kg group died or were sacrificed in extremis; 4 of 20 birds dosed with 5 mg/kg died or were

sacrificed in extremis. During recovery, an additional 5 birds died: 4 in the group dosed with 5.0 mg/kg and 1 in the group dosed with 10 mg/kg.

3. Clinical signs of toxicity. The birds dosed with pirimiphos-methyl showed signs of abnormalities in their gait which included "quietness, weakness, sluggish movements, ruffled feathers, wing drooping, stumbling, unsteadiness, leg stiffness, and exaggerated leg movements." None of these signs were reported in the group dosed with 0.5 mg/kg/day. Other signs reported included gurgling noises.

Ataxia was assessed using the criteria appended. The bird was held by its wings 0.5 to 1.0 m above a passage floor and released. The bird then walked toward its pen and had to jump up to a crate (32 cm high) and off again to reenter its pen.

Using this method of assay, no consistent signs of ataxia were reported by the laboratory results in any of the negative control groups or the hens treated with pirimiphos-methyl. The hens treated with TOCP developed the ataxia as expected.

Inspection of Appendix 6B of the study report indicates that several of the signs listed in the ataxia assessment were evident in the hens treated with pirimiphos-methyl (these are listed and underlined in the first paragraph of this section above).

4. Pathology. The birds were sacrificed by pentobarbitone injection and were perfused with 10% neutral buffered formalin while under anethesias. The head, spinal column and sciatic nerves were preserved in the formalin and the following samples were taken for histology:

Optic nerves
Olfactory nerves
Forebrain
Mid- and hind brain
Upper cervical spinal cord) one cross section and
Lower cervical spinal cord) two longitudinal sections
Thoracic spinal cord) at each level
Lumbar spinal cord)
Dorsal root ganglia
Proximal sciatic nerve
Distal sciatic nerve
Tibial nerve (distal branches)
Myoneural junction (taken at termination and from some sporadic mortalities but not examined)

APPENDIX 5

Key to points scoring system used in ataxia assessment

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0. No ataxia.

1. Doubtful; slight inco-ordination, not always apparent.

2. Slight inco-ordination; occasional stumbling or wing-dropping especially after exertion.

3. Frequent inco-ordination or stumbling, especially on alighting or after exertion.

4. Staggering gait, tail and leg reflexes may be affected; bird lands awkwardly.

5. Continuous staggering gait, bird rests often; tail and leg reflexes usually noticeably affected.

6. Bird stands for short periods only, normally moves by shuffling on hocks; tail and leg reflexes usually noticeably affected.

7. As 6; weakening limb movements; reflexes markedly affected.

8. Bird unable to stand, weak limb movements; tail and leg reflexes virtually non-existent.

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APPENDIX 11

(continued)

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Key to grading scheme in individual bird reports and summary tables

Grade I	No white matter abnormality detected.
Grade II	Disruption or fragmentation of occasional axons. Myelin abnormalities are rare. In general, on any slide of the spinal cord (two longitudinal and one transverse sections), the numbers of altered/degenerate fibres detected varied from one to approximately four. On a slide of peripheral nerve, one or two degenerate fibres were included in this grade.
Grade III	Disruption, fragmentation and distortion of a few axons, most of which were more intensely argyrophilic than the residual normal axons. Changes in myelin sheaths were minimal and usually consisted of small spheroids. In general, slides of cord with five or more, and slides of peripheral nerve with three or more degenerate fibres were recorded in this grade.
Grade IV	Qualitatively similar changes described for Grade V (see below) but affecting only moderate numbers of axons. Extent of change greater than in Grade III.
Grade V	Disruption, fragmentation and distortion of many axons, some of which are more argyrophilic on silver staining than normal axons. Considerable variation in thickness of affected axons with occasional large axon balls. Distortion and fragmentation of myelin sheaths in affected areas with variable numbers of myelinophages. A mild glial/Schwann cell response was occasionally present in the most severely affected areas. In general the extent/distribution was widespead.

These samples were then processed through differing grades of Industrial Methylated Spirit toulene to paraffin.

Histological sections were reported as being cut at 8 um and stained with haematoxylin and eosin. Additional sections from each block were stained with Glees and Marsland method for axons* and with Solochrome Cyanin for myelin**.

* Marsland, T. A., Glees, P. and Erikson, L. B. 1954, J. Neuropath. Exp. Neurol. 14, 587.
** Page, K. M., 1970, J. Med. Lab. Technol. 27, 1

Slides were prepared from hens which survived the 90-day dosing period only. The hens which died were not included because of problems related to autolysis. The birds from groups 5 and 7 were not prepared for histology. The grading criteria used to assess neuropathology is appended. Grades I and II are considered to represent background variation.

The birds dosed with TOCP produced many instances of grade III, IV neuropathology in the sections prepared from the spinal cord to clearly indicate a neurotoxic effect of this agent.

There was a single incidence of grade III neuropathological gradings in the birds treated with pirimiphos-methyl (at 10 mg/kg/day). This was considered to be incidental.

5. Recovery - The birds in groups 9 and 10 which were set aside to recover from any effects of pirimiphos-methyl showed a regain in lost body weight. In some cases it took 4-16 days for the birds to recover from the signs of toxicity due to pirimiphos-methyl. No histopathology was conducted on the hens which were allowed to recover.

CONCLUSION: This study is CORE GUIDELINES. This study demonstrates that pirimiphos-methyl at dose levels up to and including 10 mg/kg/day for 90 doses does not induce a typical (TOCP type) delayed neurotoxicity. Although some signs of ataxia-like symptoms were noted, these were not followed up by histopathological findings. The TOCP treated hens had both well defined ataxia and clearly defined neuropathological lesions in the spinal cord sections.

An examination of pirimiphos-methyl using the mammalian cell transformation test

Central Toxicology Lab. CTL/P/827, February 14, 1983
EPA Acc. No. 071451, Tab. C2

This study investigated the effects of pirimiphos-methyl over the range of 0.023 to 230 ug/ml for its ability to transform mammalian cells (baby hamster kidney fibroblasts) into a malignant type. Pirimiphos-methyl and the positive control were assayed in vitro in the presence of the S-9 liver microsome preparation only (a study without S-9 metabolic activation was not conducted).

As indicated by the data as presented, pirimiphos-methyl did not show evidence of causing increases in the frequencies of transformations. The positive control (acrylonitrile) produced the expected positive response.

TB considers this study an acceptable ~~as~~ demonstration of a negative response for the transformation assay using the S-9 activation system.

Cytogenic Study in rats of Pirimiphos-methyl

Inveresk Research International, # 412212, May 1980, EPA Acc. No. 071451, TAB C3.

This study consisted of an assessment of the ability of pirimiphos-methyl to induce aberrations in rat bone marrow cell chromosomes. Both acute and subacute dosing tests were run. In the acute study, male Charles River CD rats (10 per group) were dosed with either 0, 32, 102 or 320 mg/kg of pirimiphos-methyl or 250 mg/kg of ethylmethanesulfonate. 4 or 20 hours after dosing (or 2 hours before sacrifice) the treated rats were dosed with 3 mg/kg colchicine. One femur from each rat was excised and bone marrow was extracted and later fixed in methanol "glacialacetic."

The subacute study consisted of dosing (10 rats per group) rats with either 0, 32, 102, 320 mg/kg of pirimiphos-methyl or 100 mg/kg of ethylmethanesulfonate for 5 consecutive days. For this study a single (6 hour) sample was prepared for microscopic analysis of the femur bone marrow. The types of abnormalities looked for were: gaps, breaks, fragments, dicentrics, translocations and pulverisation. In most cases (where it was possible), 50 cells "with well spread chromosomes" were examined and scored for each rat.

Results:

Analysis of the test material as prepared for use indicated that the material was considerably lower (25% or more) than the desired level. No explanation for this was found. However, the laboratory maintained that because the rats showed signs of intoxication due to pirimiphos-methyl the doses used were sufficiently high enough to continue the assay.

No differences in the aberrations noted were found in the acute study at either 6 or 24 hours. The positive control gave a positive response (weak in the opinion of this reviewer).

In the subacute study, the high dose test group showed a statistically significantly different increase in chromosomes with gaps. No other chromosomal aberrations were found in the pirimiphos-methyl treated rats. The positive control treated rats had increases in chromosomal gaps as well as other types of aberrations. The testing laboratory interpreted the increase in gaps as due to non-specific toxicity of pirimiphos-methyl.

This study presents information that pirimiphos-methyl does not induce chromosomal aberrations in the same manner that the positive control does. The gaps induced by pirimiphos-methyl are not considered to be a mutagenic effect by TB.

GFU 053, A 75.4% W/W Formulation of Pirimiphos-methyl. (Acute toxicity and sensitization).

Huntingdon Research Lab. # ICI/356, -357, -358, -360, /SE, SS, AC/80549, March 30, 1981. EPA Acc. No. 071451, Tab. 4C.

A. Assessment of the acute oral toxicity to rats (Jan.-Feb., 1980).

5 groups of 10 rats (5 males and 5 females) were dosed with either 0, 1.0, 1.6, 2.0 or 2.5 ml/kg of test material (GFU 053) and observed for 14 days. The rats were fasted prior to dosing.

LD_{50}'s of 2.1 (1.9 to 2.5) ml/kg for both sexes.
2.0 (1.4 to 2.8) ml/kg for males
2.2 (1.8 to 3.0) ml/kg for female
were determined.

Signs of intoxication included: abnormal gait (waddling), increased salivation, ptosis; at higher doses: diarrhoea, lethargy, decreased respiratory rate, fine body tremors, ataxia (one male) and diuresis (in a male and a female). Deaths occurred within 46 hours of dosing. Autopsy revealed congestion of several organs.

The study is CORE GUIDELINES. Tox Cat. III is supported.

B. Assessment of the acute dermal toxicity to rabbits (May - July, 1980).

Two groups of rabbits were dosed with test material (GFU053). The first group consisted of 4 males and 4 females

and was dosed with 3.2 ml/kg. The second group consisted of 5 male rabbits which were dosed with 2.0 ml/kg.

4 of the males dosed with 3.2 ml/kg died or were killed during the first week of the post-mortem treatment. The females survived the 14-day observation period. None of the males dosed with 2.0 ml/kg died. The rabbits which died as a result of treatment exhibited internal hemorrhages and died three to six days after dosing. Some of the symptoms of intoxication noted were lethargy, increased respiratory rate, abnormal body carriage (hunched posture), fine body tremors, mucoid discharge from the anus. The survivors were reported as being completely recovered 14 days after dosing.

LD_{50} of >3.2 ml/kg for females
LD_{50} of between 2.0 ml/kg and 3.2 ml/kg for males.

This study is CORE MINIMUM, sufficient data to classify this product into Tox Cat. III were generated. Note: data on dermal reactions were also reported; some signs of persistent irritation were evident to the 14th day.

C. Assessment of the irritant effects on rabbit skin (February 1980).

Six New Zealand White rabbits were prepared by clipping and abrading and dosed with 0.5 ml of test material (GFU 053) in each of two intact and abraded sites. The test material was kept in place for 24 hours and the skin reactions were noted at 24 and 72 hours after treatment.

A PII of 3.8 was determined. All skin reactions were reported to have been resolved 12-14 days posttreatment.

This study is CORE GUIDELINES. Tox Cat. II is supported.

D. Assessment of irritant effects on the rabbit eye (February, 1980).

0.1 ml of test substance (GFU053) was instilled into a single eye of each of 9 rabbits. The eyes of 3 of the treated rabbits were rinsed 20-30 seconds after instillation. The eyes were examined at 24, 48 and 72 hours and 4, 7, 14, 18 and 21 days after treatment.

Corneal opacity developed in rabbits that were not rinsed. The opacity regressed by 14 days for most rabbits but in a single rabbit (with iritis), the opacity persisted to 21 days.

This study is CORE GUIDELINES. The product may be classified into Tox Cat. II.

E. Assessment of skin sensitization potential (January, March, 1980).

Two groups of 10 male guinea pigs were used in this study. The test group was prepared by clipping and induced by making 9 applications of 0.5 ml of test material (GFU 053), 50% v/v in distilled water applied on a gauze patch was used for the first 4 applications. A 30% v/v preparation was used for the later 5 applications. The induction phase was made over a 3-week period with 3 applications being made each week. The challenge phase was made two weeks after the last induction and consisted of an application of 0.5 ml of 15% v/v test material kept in place for 24 hours. The ten guinea pigs in the control group were also dosed with 15% GFU 053 at the challenge phase.

Signs of erythema and oedema resulted during the induction phase and the concentration of the GFU053 was lowered. Some signs of erythema developed after challenge, but these were not considered to be a positive response by the test laboratory.

This study is CORE MINIMUM. No positive control was included. Under the conditions of this study formulation GFU 053 was not shown to be a sensitizer to guinea pigs.

Pirimiphos-methyl (75.4% wt/wt) Formulation GFU053- Four hour exposure by inhalation in the rat

Central Toxicology Lab., # CTL/P/602, Feb. 3, 1982, EPA Acc. No. 071451, Tab. 5C

Two groups of 16 rats (8 males and 8 females) were used for this study; one group served as the control, the other as the test group. The test rats were placed into an exposure chamber into which air containing the test material (GFU053) was introduced. The test material was introduced by bubbling (10 l/min) of air through a sample volume of the liquid test material. The procedure states that "aerosolization was prevented by inclusion of a quartz wool plug." The atmospheric concentration was determined by weighing the sample of test material before and after the experiment or determining the weight loss during exposure. Using this method, it was determined that the atmospheric concentration was 0.75 mg/l. The test rats were exposed for 4 hours, the control rats were exposed to air alone.

No rats died as a result of the exposure. Only rather mild and somewhat indefinite reactions were reported in the rats exposed to GFU053. Blood plasma ChE was not affected in females (immediately after exposure) but males were reportedly

reduced. No differences in blood RBC ChE were reported. No consistent changes in gross necropsy observations were noted.

This study is CORE SUPPLEMENTARY. No accurate estimate of the atmospheric concentration of the test material was provided. The "quartz plug" could have prevented the test material from entering the chamber. The test level used did not produce signs of intoxication and this study does little to define the expected toxicity of pirimiphos-methyl by the inhalation route.

John Doherty 7/11/83

John Doherty, Ph.D.
Toxicology Branch
Hazard Evaluation Division (TS-769)

7/11/83

7/11/83

DCR-11176:JohnDoherty:7/8/83:CM#2:Rm814B:TOX-24:557-3713:efs
REVISED:07/11/83:DCR-11173:07/11/83

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